REMARKS

I. Status of Claims.

This application has been reviewed in light of the Office Action dated August 8, 2003. Of pending Claims 1-25, claims 15, and 17-25 have been withdrawn without prejudice. New claims 26 and 27 have been added to further emphasize Applicant's invention. Claims 1, 8 and 16 have been amended in a manner that is believed to overcome the rejections contained in the pending Office Action. Support for the amendments and new claims is found throughout the specification and drawings but especially on pages 15-21.

In particular, Claim 1 has been amended to specify the identification of a therapeutic compound based on a functional SNP that is identified from "individuals chosen substantially at random" from a "general population without any selection criteria" and that a gene carrying such SNP encodes a "polypeptide with a functionality selected from increased, reduced or suppressed biological activity", that the presence of such an SNP in the gene can result in "increased, reduced or suppressed expression by such gene" or results in "at least one change in the biological activity of the polypeptide encoded by said gene" all when "compared to the functionality of a polypeptide encoded by said pre-selected gene without said SNP or the functionality of said preselected gene without said SNP whereby said therapeutic compound comprises said polypeptide encoded by said gene with the SNP identified in step e), or said gene with said SNP, or a molecule capable of functionally interacting with either of said foregoing polypeptide or gene". Thus, in addition to directly creating new, desireable therapeutic molecules with altered functionality, such SNPs containing genes and their resultant polypeptides can also be used for the identification of diagnostic/prognostic or therapeutic targets

or for the identification of a protein useful as an active ingredient in a medicament. The amendments to claim 1 and the newly added claims find support throughout the specifications, figures and originally filed claims and in particular on pages 15-16, page 17 at lines 26-29, and page 30 lines 3-5.

II. Claim Rejections 35 USC 112, second paragraph.

The Examiner rejected claims 8 and 16 under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 8 has been amended by deleting the phrases within the parentheses to thereby render the claim definite within the meaning of 35 USC 112, second paragraph.

Claim 16 has been amended to emphasize how a map of genetic markers according to the invention may be generated. Applicant respectfully suggests that the indefinite rejections have been overcome by these amendments and would respectfully request that they be withdrawn.

III. Priority.

Applicant has attached to this response a translation of the French Application number 0015838 filed December 6, 2000 as the Examiner has suggested.

IV. Claims 1, 3-5, 8-9 and 16 rejected under 35 USC 102(b).

The Examiner rejected claims 1, 3-5, 8-9 and 16 under 35 USC 102(b) as being anticipated by Drysdale et al. (PNAS, Vo. 97, No. 19, pages 10483-10488, September 12, 2000)("Drysdale"). Applicant respectfully traverses this rejection.

A. Examiner's Rejection: The Examiner stated that Drysdale teaches selecting the human B2-adrenergic receptor gene, providing a sample of individuals from an index repository of "apparently normal individuals", isolating the B2AR gene, identifying thirteen SNPs in the

B2AR gene which were organized into 12 haplotypes and performing an analysis of protein and mRNA expression to determine functionality. The Examiner further stated that Drysdale teaches sampling "normal individuals" from a repository consisting of 23 Caucasian, 19 African Americans, 20 Asians, and 15 Hispanic Latinos. These individuals do not have any particular genotype or phenotype which is "known". The Examiner also stated that Drysdale teaches using the reference sequence for the intronless human B2AR gene. The Examiner suggested that Drysdale teaches identifying 8 SNPs in the 5' UTR and 5 additional SNPs, three of which alter the encoded residues in the protein and that Drysdale discloses that the PCR products from the B2AR gene were placed in a vector and receptor expression was determined by radioligand binding, and mRNA levels were determined using ribonuclease protection assays. The Examiner further stated that Drysdale also discloses that for both protein and mRNA expression, the results of the study are entirely consistent with the *in vivo* findings. Drysdale concludes that the results indicate that the unique interactions of multiple SNPs within a haplotype ultimately affect the biologic and therapeutic phenotype. On this basis, the Examiner rejected the above claims as being anticipated by Drysdale.

B. Deficiencies of Drysdale: Drysdale investigated whether two beta 2 adrenergic receptor haplotypes displayed significant differences in the *in vivo* response to the agonist albuterol (p. 10487 column 1), however, Drysdale did not disclose "functionality of the SNP identified" nor did he suggest first searching "individuals chosen substantially at random from the general population without any selection criteria" for functional SNPs to identify those that result in polypeptides with "a functionality selected from increased, reduced or suppressed biological activity" or for those resulting in "increased, reduced or suppressed expression by said gene", or for those which result in "at least one change in the biological activity of the [encoded]

polypeptide" when compared to the gene without the SNP, eg the wild type as required by Applicant's claim 1 and thus also by claims 3-5, 8-9 and 16 which directly or indirectly depend therefrom, as well as newly added claims 26 and 27.

In Drysdale, the protein expression (see Drysdale figure 3) and mRNA levels (see Drysdale figure 4) do not permit the determination of the functionality of any SNP in the β_2ARs but are relative to two β_2ARs haplotypes. This analysis is supported by Drysdale's disclosure which states: "Our current results with haplotypes are different from those previously obtained with individual SNPs taken out of context of a verified haplotype."

Therefore, Drysdale did not describe a method for determining at least one functional SNP in a gene, said SNP being isolated from a "sample population comprising a significant number of individuals chosen at random from the general population without any selection criteria" (see claims 1, 26 and 27; emphasis added). Contrary to the direction of inquiry and approach specified by Applicant's claimed invention, Drysdale statement that "This finding emphasizes the importance of studying SNPs *in vitro* within the context of a validated haplotype" (p. 10487 column 2) would have discouraged one skilled in the art from focussing on individual SNPs, particularly functional SNPs, for finding new 'nature induced' therapeutic/diagnostically useful molecules. Such molecules may have increased potency, decreased side effects or other combinations of changed functional activity making them preferred over the wild-type molecules.

The Federal Circuit has clearly enunciated that: Anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, arranged as in the claim. Lindermann Maschinenfabrik GMBH v. American Hoist and Derrick Co., 221 USPQ 481, 485 (Fed Cir. 1984) (emphasis added). Here the requirement of showing each and

every element of Applicant's claimed invention in a single prior art reference has not been met, and accordingly Drysdale fails to disclose or teach Applicant's claimed invention. It is respectfully requested that this 35 U.S.C. §102(a) rejection be withdrawn.

V. Claims 1-5, 8 and 16 rejected under 35 USC 102 (a)

The Examiner rejected claims 1-5, 8 and 16 under 35 USC 102(a) as being anticipated by Nandabalan et al.(WO 00/50436, August 31, 2000) ("Nandabalan"). Applicant respectfully traverses this rejection.

A. Examiner's Rejection:

The Examiner stated that Nandabalan teaches a method of identifying functional SNPs in a gene; that Nandabalan selects a candidate gene, namely tissue necrosis factor receptor (TNFR1); and that Nandabalan samples a "normal population" of individuals whose genomic DNA was isolated from an Index Repository containing 150 human individuals. The Examiner further stated that Nandabalan teaches isolating nucleic acid from the individuals using PCR primers and identifying at least one SNP within the nucleic acid, and that Nandabalan also identifies which of the mutations change the coding sequence, therefor which SNPs are functional. Nandabalan apparently teaches that allele-specific oligonucleotide primers may be used to detect TNFR1 gene polymorphisms and that the effects of the identified polymorphism on TNFR1 expression may be investigated by preparing recombinant cells. Nandabalan also provides Table 4 indicating observed genotypes and haplotype pairs for TNFR1, Figure 4 illustrates the SNPs within the coding sequence, and Figure 5 identifies the SNPs which alter the protein sequence.

The Examiner concluded that the SNPs which alter the protein sequence are functional to the extent that the protein sequence is altered, (i.e. modifies the functionality of the pre-selected

candidate gene). The Examiner rejected Applicant's claims on the basis that Nandabalan is anticipatory. Applicant respectfully traverses this rejection.

B. Deficiencies of Nandabalan: While Nandabalan selects a candidate gene (TNFR1), identifies SNPs in said gene and identifies which mutations change the coding sequence (figures 4 and 5), Nandabalan does so for the purpose of using such molecules as new targets and to gain an understanding of which patients may benefit from therapeutic regimens and why others may not respond. (See for example his description on page 3 lines 16-20, page 14 lines 7-10, page 26 lines 28-34). Nandabalan does not identify whether a functional SNP induces an "increased, reduced or suppressed biological activity" for the purpose of identifying new therapeutic compounds as claimed by Applicant.

Although Nandabalan discloses that "effects of the polymorphisms identified herein on expression of TNFR1 may be investigated by preparing recombinant cells and/or organisms, preferably recombinant animals, containing a polymorphic variant of the TNFR1 gene" (lines 29-31 p. 15) and that "such recombinant cells can be used to compare the biological activities of the different protein variants" (lines 11-12 p. 16), Nandabalan does not disclose systematically investigating the "functional[ity] of [an] SNP" in order to identify new "therapeutic compounds" which "comprises said polypeptide encoded by said gene with the [functional] SNP", or "said gene with said SNP, or a molecule capable of functionally interacting with either of said foregoing polypeptide or genes" as required by claim 1 and thus dependent claims 2-9 and 16.

Applicant respectfully submits that Nandabalan Table 3 (SNPs in the TNFR1 gene) and Table 4 (haplotype pairs observed in the studied population) disclosures are without consideration of whether the identified SNPs are functional or not. Although Nandabalan envisions studying the expression and biological function of TNFR1 (p. 3 lines 2-4 and lines 16-

18) and identifying drugs targeting TNFR1 protein for the treatment of disorders related to its abnormal expression or function (p. 4 lines 19-24) (i.e. molecules interacting with TNFR1 protein in order to restore a normal expression and biological function), he does not teach analyzing the "functionality" of the SNPs, an important element of Applicant's claimed invention. In short, Nandabalan's focus on detecting SNPs for purpose of understanding how to interact with said resultant patient differences is quite different and accordingly falls short of disclosing each and every element of Applicant's claimed invention focused on finding new therapeutic compounds resulting from such SNPs.

Additionally, Nandabalan notes that information on the combination of polymorphisms in the TNFR1 gene: may have diagnostic applications (level of drug response, susceptibility to disease) (p. 3 lines 18-20) and may be useful for studying population diversity, anthropological lineage, significance of diversity and lineage at the phenotypic level, paternity testing, forensic applications (p. 3 lines 18-20, p. 6 lines 14-18).

However, these are "classical" uses for polymorphisms which are generally well known in the prior art. Unlike Applicant's claimed invention, nowhere in the description of Nandabalan is there disclosed the importance of identifying functional SNPs from a "general population" in order to use such differences as a source to "identify new therapeutic compounds." Applicant respectfully submits that Nandabalan consequently fails to anticipate the method of amended claim 1 or the claims dependent thereon and therefore respectfully requests that this rejection be withdrawn.

VI. Claims 1, 3-5 and 8-9 rejected under 35 USC 102(a)

The Examiner rejected claims 1, 3-5 and 8-9 under 35 USC 102(a) as being anticipated by Gu et al. (JBC Papers in Press. Published on January 9, 2001 as Manuscript M010353200) ("Gu"). Applicant respectfully traverses this rejection.

A. Examiner's rejection: The Examiner stated that Gu teaches a method of determining at least one functional SNP in a gene by selecting a candidate gene, namely P2X7 receptor, sampling a "normal population" isolating nucleic acid from the individuals, identifying at least one SNP and identifying functional SNPs. It was further argued that Gu teaches studying PO2X7 by sequencing DNA coding for the carboxyl terminal tail of P2X7. Among other things Gu concludes that the "data in this study shows that the function of the human P2X7 receptor is affected by the single nucleotide mutation of adenine to cytosine at position 1513 of cDNA which changes glutamic acid to alanine at amino acid position 496". The Examiner stated that since Gu teaches every limitation of the instant claims, Gu anticipates the claimed invention. Applicants respectfully traverse this rejection.

B. Inapplicability of Gu: Gu is a manuscript that was published on January 9, 2001. Applicant's application claims the benefit of prior French application No 0015838 filed on December 6, 2000, a certified copy of which is attached hereto. Accordingly, the Gu et al. article, which was published after Applicant's priority date, does not constitute prior art. Applicant accordingly requests that this rejection be withdrawn.

VII. Claims 6, 10-11 rejected under 35 USC 103(a)

The Examiner rejected claims 6, 10-11 under 35 USC 103(a) as being unpatentable over Drysdale or Nandabalan or Gu in view of Apffel et al. (U.S. Patent No. 6,379,889) ("Apffel"). Applicant respectfully traverses this rejection.

A. Teachings of Drysdale: The Examiner stated that Drysdale teaches analyzing various combinations of SNPs to identify those with functionality. In particular Drysdale teaches selecting the human B2-adrenergic receptor gene, providing a sample of individuals from an index repository of "apparently normal individuals", isolating the B2AR gene, identifying thirteen SNPs in the B2AR gene which were organized into 12 haplotypes; and analysis of protein or mRNA expression to determine functionality. The Examiner further stated that Drysdale teaches sampling "normal individuals" from a repository consisting of 23 Caucasians, 19 African Americans, 20 Asians, and 15 Hispanic Latinos. These sampled individuals do not have any particular genotype or phenotype which is "known."

B. Teachings of Nandabalan: The Examiner stated that Nandabalan teaches a method of identifying functional SNPs in a gene; that Nandabalan selects a candidate gene, namely tissue necrosis factor receptor (TNFR1) and that Nandabalan samples a "normal population" of individuals whose genomic DNA was isolated from an Index Repository containing 150 human individuals. The Examiner further stated that Nandabalan teaches isolating nucleic acid from the individuals using PCR primers, identifying at least one SNP within the nucleic acid and determining whether the mutations change the coding sequence, thereby identifying which SNPs are functional. It was proffered that Nandabalan teaches that allele-specific oligonucleotide primers may be used to detect TNFR1 gene polymorphisms and that the effects of the polymorphism identified on expression of TNFR1 may be investigated by preparing recombinant cells. Nandabalan's Table 4 indicates observed genotypes and haplotype pairs for TNFR1; Figure 4 illustrates the SNPs within the coding sequence; and Figure 5 illustrates the SNPs which alter the protein sequence.

The Examiner concluded that the SNPs which alter the protein sequence are functional to the extent that the protein sequence is altered, (i.e. modifies the functionality of the pre-selected candidate gene.

C. Teachings of Gu: As earlier described Gu is not prior art and his teachings are therefore inapplicable.

D. Teachings of Apffel: The Examiner stated that Apffel et al. (Apffel) describes multiplexing methods for identifying nucleic acids using denaturing liquid chromatography.

E. Deficiencies of Cited References: As described in the cited references above, as far as the area of diagnostic and therapy is concerned, SNPs have mainly been used in genomic studies to obtain markers to investigate and diagnose genetically linked diseases. Applicant's claimed invention is an inventive method to produce new medicaments or valuable targets for diagnostic/prognostic or therapy based on genetic alterations discovered in the general public as opposed to individuals suffering diseases or abnormal condition.

The conventional approach has been to begin with "diseased" individuals and then to study their genetic make-up in the hope of identifying a genetic cause, such as an SNP, with the hope of then being able to develop a therapeutic which combats or counteracts the effect of the SNP. In contrast, the current invention begins with a normal population of individuals in the hope of identifying individuals with SNPs which have functional effects to thereby identify successful mutations in the population whereby such individuals are 'super' normal and possess 'advanced' versions of known molecules. This new approach is predicated on the belief that nature is far more advanced than man in its experimentation to develop superior therapeutically effective molecules. The instant invention is focussed upon taking advantage of this novel

perspective. In stark contrast, the cited references do not, either separately or in combination, make Applicant's claimed approach obvious.

Drysdale and Nandabalan have been previously addressed. Apffel merely describes one of the methods set forth in Applicant's claim 6 that can be used to carry out step d) of claim 1. However Appfel adds nothing to the deficiencies of Drysdale and Nandabalan regarding the method of claim 1, upon which claim 6 depends. Because it is submitted that claim 1 is novel and inventive, thus also claim 6 regardless of the teaching of Apffel.

Specifically, no teachings within Drysdale, Nandabalan, or Apffel suggest any manner of their combination to lead to Applicant's method for drug discovery wherein the "functionality of said SNP" is being used for the identification of new therapeutic compounds wherein said functionality of the SNP induces a" increased, reduced or suppressed biological activity" in the encoded polypeptide or the gene and where the "therapeutic compound comprises the polypeptide encoded by the gene with the SNP", or the "gene with the SNP" or a "molecule capable of functionally interacting" with either. (see claim 1 from which claim 6 depends and claim 10, from which claim 11 depends. Simply put, none of the cited references, whether taken alone or in combination, arrive at the subject matter of Applicant's claimed invention.

The rejection has further failed to provide any rational (apart from Applicant's own disclosure) for combining the cited references. Such use of Applicant's own disclosure is improper. Indeed, well-established legal principles, provide:

> *"That one skilled in the art is not synonymous with obviousness.... That one can reconstruct and/or explain the theoretical mechanism of an invention by means of logic and sound scientific reasoning does not afford the basis for an obviousness conclusion unless that logic and reasoning also supplies sufficient impetus to have led one of ordinary skill in the art to combine the teachings of the reference to make the claimed invention"* Ex parte Levengood, *28 USPQ 2d 1300 (Bd. Pat. App. & Inter. 1993).*

No reference has been offered suggesting the manner of combination as postulated by the Examiner. None of the references, alone or in combination, provide "sufficient impetus" to support the combination that the Examiner makes to effect the obviousness rejection. Only Applicant's own disclosure could provide this motivation and such a use of Applicant's specification is not permitted. Accordingly, it is respectfully submitted that not only is the suggested combination improper, but it also fails to teach or make obvious Applicant's invention. Applicant respectfully requests that this rejection be withdrawn.

VIII. Claims 7, 12-14 rejected under 35 USC 103(a)

The Examiner rejected claims 7, 12-14 under 35 USC 103(a) as being unpatentable over Drysdale or Nandabalan or Gu in view of Apffel et al. (U.S. Patent No. 6,379,889) ("Apffel") and in further view of Oefner et al. (US Patent 5,795,976) ("Oefner"). Applicant respectfully traverses this rejection.

A. Examiner's rejection: The Examiner stated, that while neither Drysdale, Nandabalan, Gu nor Apffel specifically teach a method of identifying SNPs using DHPLC followed by sequencing or mini-sequencing, Oefner teaches a method of performing DHPLC to identify sequence variations followed by allele specific PCR to confirm the sequence. Oefner subsequently confirmed that polymorphic site identification by subsequent conventional sequencing techniques. It is the Examiner's position that it therefore would have been *prima facie* obvious to one of ordinary skill at the time of the invention was made to have performed DHPLC to detect SNPs, as taught by Drysdale, Nandabalan, GU and Apffel followed by sequencing as taught by Oefner. The Examiner further stated that it would have been *prima*

facie obvious to one of ordinary skill at the time the invention was made to confirm the polymorphic site identification by using conventional sequencing techniques as specifically taught by Oefner. Applicant respectfully traverses this rejection.

B. Deficiencies of Cited References: Applicant respectfully submits that the deficiencies of the cited references, as previously discussed, are not cured by the additional Oefner disclosure and that this new combination still fails to make obvious Applicant's claimed invention. Gu is not prior art.

There is a complete absence of any direction within the teachings of Drysdale, Nandabalan, Gu, Apffel and Oefner that would suggest either the cited combination specifically or a method for drug discovery wherein the functionality of the SNP is used to identify new therapeutic compounds based on functionality of said SNP which induces a change in expression, activity, and/or localization of the encoded protein as generally set forth in claims 1 and 10 from which claim 7 and claims 12-14, respectively depend.

Applicant concedes that these references deal with various aspects of SNPs generally, but, Applicant is not claiming SNPs. Rather, Applicant has discovered a new way of approaching the problem of identifying new therapeutically useful compounds. This new method entails first selecting the compound (e.g. receptor, hormone, cytokine or other known therapeutic agent) of general interest for which an improved therapeutic is desired, then evaluating a plurality of copies of the respective encoding gene obtained from a random selection of individuals representative of a population to detect the presence of SNPs in the encoding genes, and identifying those genes with SNPs which result in compounds having functionality which is altered from that of the 'wild-type' compound. This approach to finding the 'benefits' of nature's experimentation via SNP induced variations differs remarkably, and unobviously,

from the classical approach exemplified by the cited art. Such conventional approaches study SNP induced disease conditions in an attempt to try to design an ameliorative therapeutic compound to combat the SNP induced error or condition. It is accordingly understandable that Applicant's invention as claimed is therefore neither disclosed nor made obvious by the references of record.

None of the cited references, whether taken alone or in combination, arrive at the subject matter of Applicant's claimed invention. Applicant respectfully request that this rejection be withdrawn.

CONCLUSION

Applicant respectfully requests expeditious consideration and passage of the present application to issuance. The Examiner is invited and encouraged to telephone the undersigned if she believes such would facilitate prosecution of the present application.

Respectfully submitted,

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Dated: November 7, 2003